Augmented Renal Clearance

Implications for Antibacterial Dosing in the Critically Ill

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Abstract

The prescription of pharmaceuticals in the critically ill is complicated by a paucity of knowledge concerning the pharmacokinetic implications of the underlying disease state. Changes in organ function can be dramatic in this population, both as a consequence of the primary pathophysiology and in response to clinical interventions provided. Vascular tone, fluid status, cardiac output and major organ blood flow can be significantly altered from baseline, influencing the volume of distribution and clearance of many commonly prescribed agents.

Although measurable endpoints can be used to titrate doses for many drugs in this setting (such as sedatives), for those agents with silent pharmacodynamic indices, enhanced excretory organ function can result in unexpectedly low plasma concentrations, leading to treatment failure. This is particularly relevant to the use of antibacterials in the critically ill, where inadequate, inappropriate and/or delayed prescription can have significant effects on morbidity and mortality.

Augmented renal clearance (ARC) refers to enhanced renal elimination of circulating solute and is being described with increasing regularity in the critically ill. However, defining this process in terms of current

measures of renal function is problematic, as although the glomerular filtration rate (GFR) is largely considered the best index of renal function, there is no consensus on an upper limit of normal. In addition, the most readily available and accurate estimate of the GFR at the bedside is still widely debated. From a pharmacokinetic point of view, ARC can result in elevated renal elimination and subtherapeutic plasma concentrations of pharmaceuticals, although whether this process solely involves augmented filtration (as opposed to enhanced tubular secretion and/or reabsorption) remains uncertain.

The primary contributors to this process are likely to be the innate immune response to infection and inflammation (with its associated systemic and haemodynamic consequences), fluid loading and use of vasoactive medications. The resultant increase in cardiac output and renal blood flow prompts enhanced glomerular filtration and drug elimination. Current evidence suggests that young patients without pre-existing co-morbidity or organ dysfunction who present with trauma are most likely to manifest ARC. As this phenomenon has received little attention in the literature, dose modification has rarely been considered.

However, with increasing data supporting the concept, and many investigators demonstrating sub-therapeutic concentrations of drugs in the critically ill, consideration of ARC and alternative dosing regimens is now mandatory, both to improve the likelihood of treatment success and to reduce the rate of development of antibacterial resistance.

Augmented renal clearance (ARC) in patients without organ dysfunction is being increasingly described in subsets of critically ill patients.[1-11] In the context of antibacterial therapy, ARC has the potential to result in subtherapeutic dosing, treatment failure or selection of resistant micro-organisms.[11,12] This has significant implications in patients with sepsis, whereby the consequences of inappropriate antibacterial therapy may be catastrophic.[13-16] Given the persisting high associated intensive care unit (ICU) and in-hospital mortality rates,[17] action against any pathophysiology that alters anti-bacterial efficacy should be considered mandatory. ARC is also likely to be a key mechanism underlying the high antibacterial clearances previously described in patients with significant burn injury[4,18-24] or haematological malignancy.[25-28]

Current evidence stresses that the prescription of antibacterials in critically ill patients with sepsis is complex. Pharmacokinetic variability may be significant, with fluid shifts, altered capillary permeability, impaired vascular tone, organ dysfunction and multi-organ failure all likely to alter the pharmacokinetics of many routinely prescribed agents.[29] Although ARC is a factor rarely considered in this context, it increases the likelihood of suboptimal antibacterial concentrations.

The aims of this article are to define ARC, review its significance in the critically ill and explore the underlying mechanisms within the context of methods commonly used to assess renal function. We also seek to describe those subpopulations of critically ill patients most 'at risk' from ARC and review the implications for antibacterial dosing strategies in these groups.

Data for this review were identified by searches of MED-LINE (from 1966 to January 2009) and EMBASE (from 1966 to January 2009). The search terms included 'creatinine clearance', 'antibiotics', 'pharmacokinetics' and 'critical illness'. In addition, other references were identified from the extensive files of the authors and from reference lists of identified papers.

1. What is Augmented Renal Clearance (ARC)?

A key function of the human kidney is excretion of circulating metabolites, toxins, waste products and pharmaceuticals, through a combination of glomerular filtration, tubular secretion and reabsorption. ARC refers to enhanced elimination of solute as compared with an expected baseline. However, accurately defining this process is problematic and is reliant on the accepted 'normal' values of renal function for a particular patient or population. The most widely accepted descriptor of renal function in health and disease is the glomerular filtration rate (GFR), and 'normal' values are roughly $130 \, mL/min/1.73 \, m^2$ and $120 \, mL/min/1.73 \, m^2$ in young men and young women, respectively.[30] Importantly, these values decline with age[30] (figure 1). Previously, some authors have attempted to define abnormal glomerular filtration on the basis of elevated GFRs.

Sunder-Plassmann and Horl[31] have proposed a categorization system for elevated GFRs, which they term 'glomerular hyper-filtration'. In their article, the authors defined glomerular hyperfiltration on the basis of a GFR $\geq 120 \, mL/min/1.73 \, m^2$ ($>149 \, mL/min/1.73 \, m^2$ in young adults). However, this categorization system does not differentiate between the sexes, requires further validation in the critically ill and may represent values within the normal range for some patients. In addition,
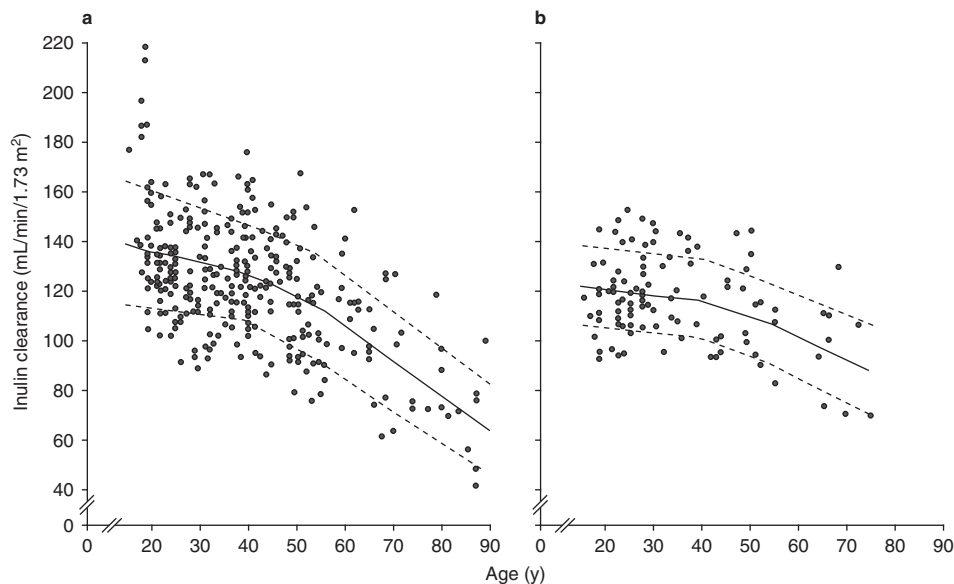
Fig. 1. Normal values of the glomerular filtration rate (GFR) in men and women. Inulin clearance for various ages in mL/min/1.73 m^2 (**a**) in men and (**b**) in women. The solid lines represent the mean values of the GFR per decade of age, and the dashed lines represent the values of 1 standard deviation from the mean. (Reproduced from Stevens et al.,[30] with permission.)

the term 'glomerular hyperfiltration' describes changes typically seen in chronic kidney disease, and may not be representative of the mechanisms in critical illness.

Our proposed definition of ARC uses values 10% above the upper limit of normal – namely, GFRs >160 mL/min/1.73 m^2 in men and >150 mL/min/1.73 m^2 in women. Albeit conservative, these cutoffs are more likely to identify patients with truly augmented clearances. In addition, as a number of separate authors have identified creatinine clearance (CL$_{CR}$) as a key pharmacokinetic covariate in predicting the clearance of many antibacterials,[5,32-41] this definition is an important step in identifying subpopulations at risk of subtherapeutic antibacterial exposure. Further work is clearly needed to refine these values and correlate them with pharmacokinetic and outcome data.

1.1 Physiological Changes in Critical Illness Likely to Contribute to ARC

The systemic inflammatory response syndrome (SIRS), a part of the innate immune response, describes a syndrome of physiological and laboratory derangements that can be recognized in the critically ill, regardless of the underlying aetiology.[42] Potential causes include trauma,[43] pancreatitis, burn injury, autoimmune disorders, ischaemia and major surgical procedures.[44] Sepsis is then defined as the presence of infection in conjunction with SIRS.[45]

The primary haemodynamic manifestations include a low systemic vascular resistance index and high cardiac output.[46] The underlying hypermetabolic and inflammatory state is driven by the release of endogenous cytokines and inflammatory mediators, in addition to the relative cellular dysoxia. How these changes impact on renal function is still being studied. In large animal models of sepsis, renal blood flow has been documented to increase in concert with cardiac output,[47] and in postoperative critically ill patients, cardiac output has been closely correlated with CL$_{CR}$.[3]

Measures to improve cardiovascular function in the critically ill commonly involve administration of intravenous resuscitation fluids and use of vasoactive medications.[48,49] Animal research has confirmed that crystalloid administration can result in an increase in CL$_{CR}$,[50] although the influence of vasoactive agents on renal blood flow is continuing to be investigated.[51] Recent experimental data suggest that norepinephrine (noradrenaline) [a commonly employed vasopressor/inotrope] acts to increase cardiac output,[52,53] renal blood flow[52] and CL$_{CR}$,[52,53] particularly in states characterized by marked vasodilation.[54] Previous studies in human sepsis and septic shock have confirmed a positive effect of norepinephrine on CL$_{CR}$.[55-57] Figure 2 schematically illustrates the potential mechanisms underlying ARC in the critically ill.

These data suggest that in critically ill patients without significant renal dysfunction and in whom adequate resuscitation has been achieved, ARC is likely to be common. However,
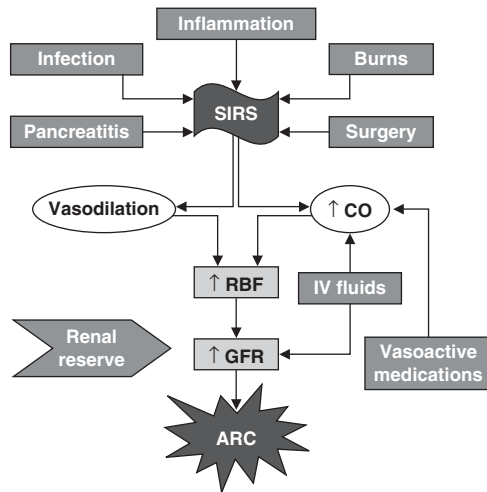
Fig. 2. Mechanisms underlying augmented renal clearance (ARC) in the critically ill. **CO** = cardiac output; **GFR** = glomerular filtration rate; **IV** = intravenous; **RBF** = renal blood flow; **SIRS** = systemic inflammatory response syndrome; ↑ indicates increase.

many patients can develop acute kidney injury with sepsis, secondary to mechanisms that are still being investigated,[58] and often in concert with significant laboratory and physiological derangement.[59] As a consequence, consideration of dose reduction of drugs in this setting may also be necessary.

1.2 Assessing the Presence of ARC in the Critically Ill

The most accurate, routinely available method of assessing the GFR is still uncertain, although serum creatinine concentrations are routinely used as an index of glomerular filtration in a clinical setting. However, isolated serum creatinine concentrations within the 'normal' reference range are insensitive indicators of the GFR in the ICU.[60] In addition, age, sex, race, state of hydration, muscle mass, metabolic state and muscle injury may all influence this value.[61] Despite these limitations, and perhaps incorrectly, acute elevations in serum creatinine concentrations are routinely interpreted as renal dysfunction, particularly in concert with oliguria (urine output <0.5 mL/kg/h).

In contrast, a 'normal' serum creatinine concentration within the laboratory reference range is assumed to equate to normal renal function, especially when the urine output is greater than 0.5 mL/kg/h. However, this interpretation of renal function may not always be correct. In patients whose protein stores or intake may be low, such as those who are elderly, malnourished, debilitated, hospitalized for long periods, or at the end of pregnancy, a 'normal' serum creatinine concentration may represent significant renal impairment. Recent work has also suggested that low baseline serum creatinine concentrations may be a risk factor for mortality in the critically ill.[62]

Numerous equations have been developed to estimate the GFR from serum creatinine values in ambulatory or ward-based patients with chronic kidney disease. The Modification of Diet in Renal Disease (MDRD) equation[63] was developed using data from 1628 patients with chronic kidney disease and calculates an estimated GFR adjusted to body surface area. Although it is a useful tool to screen for and monitor chronic kidney disease, its main limitation is in those without renal impairment, where inaccuracies have been reported at higher GFRs.[64-66] The Cockcroft-Gault equation[67] was developed in 1973 in 249 male patients and, although widely employed, has poor application in the critically ill.[60,68-70] Using historical data, Jelliffe[71] has proposed a method of estimating CL_{CR} in those with unstable renal function. Although of significant merit, this method includes a requirement for at least two serum creatinine values (usually separated by 24 hours), and it suffers from the pitfalls of measuring serum creatinine concentrations in the critically ill. Further validation in this setting is needed.

Although these equations potentially provide more useful data than serum creatinine concentrations alone, particularly in patients recently admitted to the ICU,[72] clinicians should be dissuaded from using such equations to calculate the GFR, as they ignore the important effects of disease pathophysiology. Urinary creatinine collections of 8, 12 and 24 hours have been used to determine the GFR in critically ill patients,[73-75] although a 2-hour collection may be just as accurate.[9,72] Some authors have advocated using longer collection periods to improve the accuracy of GFR estimates[76] although, given the dynamic nature of critical illness, controversy exists over the most useful time for specimen collection. This is compounded by the circadian nature of the GFR,[77] and intraindividual variability is likely to be substantial. More frequent measurement is suggested in the critically ill, as there is potential for rapid changes in organ function.

Other markers such as inulin,[78] sinistrin[79] and cystatin C[30,80] may also have benefits for estimating the GFR but have not been widely adopted in clinical practice. Thus, because of the established correlation with drug clearance[5,7] and ease of measurement in the ICU, we believe that a timed urinary creatinine collection remains the most appropriate and convenient method for identifying patients with ARC.

1.3 ARC versus Renal Tubular Secretion or Reabsorption

Although it is convenient to define ARC on the basis of an elevated GFR, it is unknown whether there is a concomitant

change in tubular secretion or reabsorption. Assessment of either component of renal function remains a difficult task, particularly as there is no specific agreed test that evaluates each process simultaneously or is routinely available. In a research context, this has prompted the administration of a 'cocktail' of different markers to characterize each process in the individual patient.[81,82] Future work is urgently needed in this area to outline any role in the critically ill.

1.4 Prevalence of ARC and Subpopulations Likely to Develop It

Although few robust studies are available, some data exist that may be instructive as to the prevalence of ARC as well as the patients most at risk. In a single-centre ICU observational study, Fuster-Lluch et al.[6] reported an incidence of glomerular hyperfiltration of 17.9% on admission to the ICU, with a mean CL_{CR} of $142\,mL/min/1.73\,m^2$. Patients with an elevated GFR were primarily multi-trauma victims or postoperative patients, were younger, and had lower Acute Physiology and Chronic Health Evaluation (APACHE) II scores and higher urine outputs.

Brown et al.[3] also demonstrated elevated CL_{CR} in a small cohort of young postoperative trauma patients, whose peak CL_{CR} values reached $190\,mL/min/1.73\,m^2$. Albanese et al.[1] documented elevated CL_{CR} in a subgroup of isolated traumatic brain-injured patients receiving norepinephrine. Significantly, clearances were elevated prior to institution of the vasopressor and remained elevated for the 24 hours of the study. A similar result was noted by Benmalek et al.[2] in their paper investigating the effects of dopamine in addition to norepinephrine in the management of post-traumatic intracranial hypertension. Recently, we demonstrated ARC in a cohort of patients with severe head injury receiving osmotherapy (hypertonic saline) and/or vasopressor infusion for the maintenance of cerebral perfusion pressure (unpublished data). The mean age of this group was 26 years, and 85% met the criteria for ARC during their ICU stay. Of note, clearances were elevated both on and off cerebral perfusion pressure therapy.

Shikuma et al.[83] have previously investigated the clearance of piperacillin in critically ill surgical patients with sepsis and normal renal function. In this relatively young cohort (mean age 44 years), wide interindividual variations were reported in key pharmacokinetic parameters, in addition to significantly elevated drug clearance. CL_{CR} values and haemodynamic parameters were not provided, although a moderate correlation was reported between drug elimination and CL_{CR}.[83] In contrast, Jacolot et al.[84] were unable to demonstrate any significant changes in the pharmacokinetics of cefpirome

administered to traumatized patients with SIRS, as compared with matched healthy controls. Estimated CL_{CR} values were elevated in the trauma group (median 147 mL/min), although this finding did not reach statistical significance. Of note, cefpirome was administered on average 9 days post-admission, no haemodynamic data were reported, and patients requiring vasopressor administration were excluded.[84]

It follows that younger patients (roughly <55 years), admitted post-trauma (particularly after head injury) or post-surgery appear to be at greatest risk of ARC. Higher antibacterial clearances have also been reported in patients with sepsis, haematological malignancy[25-28] and significant burn injury.[4,18-24,85]

1.5 Time Course of ARC

The time course of ARC in the critically ill is still uncertain, and some patients may develop this phenomenon later in their ICU admission. It is likely to vary between patients and depends on the pathophysiology of the presenting disease process and the type of clinical interventions undertaken. In the study by Fuster-Lluch et al.,[6] the authors observed that the prevalence of glomerular hyperfiltration (CL_{CR} >120 mL/min/m^2) was greatest on day 5 of the study. Brown et al.[3] reported peak CL_{CR} levels on the fourth day, with levels returning to immediate postoperative values by day 7. In our recent observational study in traumatic brain injury, peak CL_{CR} values were recorded after a mean of 4.7 days (range 0–11.5 days) of treatment (unpublished data). As the likely mechanisms involve a SIRS response, fluid loading and use of vasoactive medications,[83,86] ARC should always be considered in such a context. Where doubt exists, a timed urinary creatinine collection should be performed.

The clinical importance of ARC relates primarily to enhanced drug elimination, leading to subtherapeutic concentrations and potentially to treatment failure. Where drugs are administered to achieve a desired clinical effect (e.g. antihypertensives and sedatives), doses can be easily modified in the presence of ARC. However, for drugs with more subtle endpoints, such as antibacterials, and where the consequences of suboptimal therapy can be catastrophic, an estimate of drug clearance should be considered early to enable accurate dosing.

2. ARC as It Relates to Antibacterial Pharmacokinetics and Pharmacodynamics: Considerations for Dosing in the Intensive Care Unit

Antibacterials can be clearly classified on the basis of their bacterial kill characteristics. The β-lactam group of agents

demonstrates time-dependent killing and, as such, the time for which the drug concentration remains above the minimum inhibitory concentration (MIC) for bacterial growth (T>MIC), is the best predictor of antibacterial efficacy.[87] Maintaining adequate plasma concentrations throughout the dosing interval is therefore essential, and the implications of ARC are most notable for β-lactams. In contrast, aminoglycosides have a concentration-dependent kill characteristic, whereby the effect is determined by the ratio of the maximum plasma drug concentration (C_{max}) to the MIC (C_{max}/MIC).[88] For other agents, such as fluoroquinolones and glycopeptides, the ratio of the area under the plasma concentration time curve from 0 to 24 hours (AUC_{24}) to the MIC (AUC_{24}/MIC) is the key pharmacokinetic-pharmacodynamic factor[89,90] associated with efficacy. Although more speculative, ARC could significantly influence the pharmacokinetic profile of renally eliminated agents in this group,[11] mandating more frequent dosing.

2.1 β-Lactam Antibacterials

The β-lactam group of antibacterials includes the penicillins, cephalosporins, carbapenems and monobactams, and is the group for which the greatest amount of data exist concerning the implications of ARC. In the absence of any significant post-antibacterial effect for a given agent, dosing schedules should aim to keep plasma concentrations above the MIC for 90–100% of the dosing interval.[91] In addition, concentrations 4–5 times the MIC are ideal, as bacterial killing is maximal.[92,93]

The majority of these agents are renally eliminated (through a mixture of glomerular filtration and tubular secretion), and a number of pharmacokinetic-pharmacodynamic papers have been published using different dosing regimens in the critically ill (table I). In addition, a correlation between CL_{CR} and total drug clearance has been reported for a number of agents,[20,32,36,38-41,97,99,101,110,112,121,122] and recent work by Conil et al.[5] has highlighted the importance of CL_{CR} as a key covariate in drug elimination, with a strong inverse relationship between CL_{CR} and the minimum plasma drug concentration. Furthermore, both increased drug clearance and significant interindividual variability have been reported in the critically ill[34,40,83,95,99,109,119] (table I).

Although for some antibacterials the mean pharmacokinetic data reported for critically ill patients may not be greatly different from those in studies of healthy subjects (table I), the significant interindividual variability that is often documented indicates that summary statistics are not accurate in describing this phenomenon. In addition, as many critically ill patients manifest acute kidney injury and renal dysfunction, studies of small numbers in a heterogenous critically ill population will be underpowered to detect ARC. In those patients with normal renal function, ARC is likely to be common.[107,114]

A recent study by Noel et al.[123] involving the new, investigational, broad-spectrum cephalosporin ceftobiprole is worth consideration, as it highlights the potential clinical implications of ARC. Inferior cure rates, when compared with the combination of linezolid/ceftazidime, were documented in patients with ventilator-associated pneumonia (VAP), who were young (<45 years) or had an elevated CL_{CR} at baseline (≥150 mL/min).[123] Although the clinical implications of this work are significant, it must be regarded primarily as hypothesis generating, as the study has yet to be published in a peer-reviewed journal, and no pharmacokinetic data have been provided.

2.1.1 Carbapenems

The carbapenems (meropenem, imipenem, panipenem, ertapenem, doripenem and biapenem) are considered a separate class of β-lactam antibacterials and also demonstrate time-dependent killing.[124] *In vitro* models have suggested that the carbapenem post-antibacterial effect enables these agents to require less T > MIC[125] for bacteriostatic activity (20%) and bactericidal activity (40%).[126] As demonstrated with other β-lactams, CL_{CR} is a key covariate in predicting drug elimination,[36,37] which can be elevated in the critically ill (table I).[34,119] This in turn can lead to potentially subtherapeutic drug concentrations for large portions of the dosing interval.[34]

2.1.2 Implications of ARC for Dosing of β-Lactams

These data serve to underline the importance of ARC in dosing of β-lactam antibacterials in the critically ill and raises important questions as to the optimal strategy in this setting. Given the time-dependent kill characteristics of this class of antibacterials and the increased clearances documented in the critically ill, maintaining adequate drug concentrations through more frequent, extended or continuous dosing must be considered. Pharmacokinetic-pharmacodynamic data support administration by extended or continuous infusion,[32,103,127-133] and recent work has demonstrated improved clinical outcomes in subsets of critically ill patients, particularly VAP.[127,134-137] However, a recent systematic review of continuous dosing strategies has failed to demonstrate any clinical advantage,[138] although any role in the setting of ARC remains unknown. Despite the lack of conclusive outcome data, continuous infusion of β-lactams offers an attractive strategy to maintain therapeutic drug concentrations, and ongoing, prospective work in this area is needed to address the paucity of evidence.

Table I. Studies of β-lactam antibacterials in healthy subjects and critically ill patients

Antibacterial	Healthy subjects			Critically ill patients						
	n	antibacterial dose	CL [mL/min]^a	population	n	antibacterial dose	CL [mL/min]^a	CL$_{CR}$ [mL/min]^a	interindividual variability?	increased CL?
Cefepime	7	2 g IV[94]	138 (22)	Sepsis[39]	13	2 g IV q12h	127 (33)	130.6 (32)		
				ICU patients[95]	55	2 g IV q12h or 4 g IV CI	137.3 (45%)^b	123.2 (54.6)	✓	
				Burns[20]	13	2 g IV q8h	119.1 (59.6)	133.5 (67.4)	✓	
				Sepsis[96]	7	2 g IV	125 (51)	54.6 (7.7)	✓	
Cefpirome	9	2 g IV[84]	101.7 (85–146.7)^c	Sepsis[40]	12	2 g IV q12h	158 (88–228)^c	146.4 (72–252)^c	✓	✓
				Trauma and sepsis[84]	9	2 g IV q12h	126.7 (71.7–248.3)^c	147 (82–190)^c	✓	
				Sepsis[97]	12	2 g IV	75 (11)	69.6 (21.2)	✓	
Ceftriaxone	12	2 g IV[98]	19.8 (2.5)	Critically ill with normal renal function[99]	9	2 g IV q24h	41 (12)	114 (39)		✓
				ICU patients with normal renal function[100]	7	2 g IV q24h	26.3 (4.9)/ 1.73 m^2	93.7 (20.3)/ 1.73 m^2		✓
				Critically ill with normal renal function[101]	3	1.5 g IV	18 (5.5)	112 (29)		
Ceftazidime	12 M	1 g IV[102]	116.5 (8.8)	Burns[20]	17	1 g IV q4h	124.9 (62.6)	119.2 (53.4)	✓	✓
	12 F	1 g IV[102]	97 (6.5)	Sepsis[41]	8	2 g IV q8h	99 (28.1)	102.8 (28.5)	✓	
				Trauma[103]	31	2 g IV q8h or 60 mg/kg/day^d CI	164.5 (62.3)	IB 96.8 (21.6) CI 96.8 (23.3)	✓	✓

Table I. Contd

Antibacterial	Healthy subjects			Critically ill patients						
	n	antibacterial dose	CL [mL/min]^a	population	n	antibacterial dose	CL [mL/min]^a	CL$_{CR}$ [mL/min]^a	interindividual variability?	increased CL?
				Critically ill[104]	15	2 g IV q8h	151 (79.8)	61.1 (24.9)	✓	✓
				Melioidosis[32]	21	120 mg/kg/day^d q8h IB or CI	67.67 (5.83–185.5)^c		✓	
				Abdominal sepsis[105]	18	4.5 g IV CI or 1.5 g IV q8h	IB 85 (38.3–148.3)^e CI 68.3 (23.3–148.3)^e	IB 106 (59–160)^e CI 93 (36–215)^e	✓	
Piperacillin	6	4 g IV q8h[106]	188 (25)	Critically ill[83]	11	2.5–4 g IV	396 (286)	116.5 (55.8)	✓	✓
				Critically ill[107]	13	4 g IV q6h or q8h as IB or CI (333–500 mg/h)	1150 (1001–3530)^f	IB 199 (91–233)^f CI 166 (103–237)^f	✓	✓
				Critically ill[5]	70	4 g IV q6h or q8h		65 (6–216)^c	✓	✓
				Abdominal sepsis[38]	52	3 g IV q6h or 12 g IV CI	230 (34.6%)^b	89 (22–150)^c		✓
Meropenem	6	1 g IV[108]	254 (16)	Sepsis[109]	10	1 g IV	191 (52.2)	61.2 (37.9)	✓	
				Sepsis (CL$_{CR}$>50 mL/min)[110]	8	1 g IV q8h	155.8 (40.6)	71.1 (15)	✓	
				Septic shock[111]	6	1 g IV	112 (70)	52 (51)	✓	
				Surgical infections[112]	11	1 g IV q8h	170 (65)	50 (21.4)	✓	
				Critically ill[113]	15	2 g IV q8h or 3 g IV CI	IB 156.67 (20) CI 128.33 (23.3)	83.7 (53.1)		
				Sepsis[114]	10	1 g IV q8h or 3 g IV CI	226.7 (23.3)	CI 93 (69–161)^f IB 106 (98–127)^f	✓	
Imipenem	8	1 g + cilastatin 1 g IV[115]	186 (16)/ 1.73 m^2	Sepsis[109]	10	1 g + cilastatin 1 g IV	116.4 (42.3)	76.2 (33.67)	✓	
				Critically ill[116]	6	500 mg + cilastatin 500 mg IV q6h–q8h	105 (13.3)	34.3 (10.3)		

Continued next page

Table I. Contd

Antibacterial	Healthy subjects			Critically ill patients						
	n	antibacterial dose	CL [mL/min]a	population	n	antibacterial dose	CL [mL/min]a	CL_{CR} [mL/min]a	interindividual variability?	increased CL?
Ertapenem	16	1 g IV[118]	29.5 (3.4)	Nosocomial pneumonia[117]	20	1 g + cilastatin 1 g IV q8h or 2 g + cilastatin 2 g CI	205 (70)	CI 122 (33) IB 128 (35)	✓	✓
				Severe sepsis[119]	8	1 g IV q24h	200.5 (306.9)	96.8 (43.3)	✓	✓
				VAP[120]	15	1 g IV q24h	73.3 (63.3–81.7)f	74 (66–109)f		✓
				VAP[34]	17	1 g IV q24h	43.2 (23.7)	93.8 (52.4)		✓

a Data are expressed as mean (SD) except where indicated otherwise.

b Mean (interindividual variability).

c Median (range).

d Assuming that bodyweight is 70 kg.

e Mean (range).

f Median (interquartile range).

CI = continuous infusion; **CL** = total drug clearance; **CL$_{CR}$** = creatinine clearance; **F** = females; **IB** = intermittent bolus; **ICU** = intensive care unit; **IV** = intravenously; **M** = males; **qxh** = every x hours; **VAP** = ventilator-associated pneumonia.

2.2 Glycopeptide Antibacterials

The specific pharmacokinetic-pharmacodynamic profile of the glycopeptides is not fully understood, as some data suggest that these agents have time-dependent properties,[139-141] while animal studies have suggested that the C_{max}/MIC ratio predicts efficacy against some micro-organisms.[142] Vancomycin is the most commonly prescribed glycopeptide, and recent studies have indicated that the AUC_{24}/MIC ratio is the most important pharmacokinetic-pharmacodynamic parameter correlating with efficacy.[90,143] Clinical data have linked AUC_{24}/MIC ratios of ≥400 with superior clinical and bacteriological responses in patients treated with vancomycin for meticillin-resistant *Staphylococcus aureus* infections of the lower respiratory tract.[144]

Vancomycin is primarily renally eliminated[145] through a mixture of glomerular filtration and renal tubular secretion. A large population pharmacokinetic study has demonstrated a significant correlation between vancomycin clearance and CL_{CR}.[146] Additional work in the critically ill has confirmed this relationship[85,147,148] and suggests that CL_{CR} accounts for >50% of the variability in vancomycin clearance in this population.[35] Furthermore, higher dose requirements have been demonstrated in patients concurrently receiving vasoactive medications,[145] in addition to augmented clearances in burns patients[85] and haematological malignancy.[27] Recently, Pea et al.[148] have developed dosing nomograms for vancomycin based on CL_{CR} estimates, with good correlation between predicted and observed plasma concentrations.

Teicoplanin has a spectrum of activity similar to that of vancomycin, although its longer elimination half-life (in excess of 90 hours, due to high protein binding)[149] allows for once-daily dosing. A correlation between drug clearance and estimated CL_{CR} of this agent has been reported in the critically ill,[28,33,150] and enhanced elimination has been demonstrated in the setting of hypoalbuminaemia[33] and severe neutropenia.[28]

2.2.1 Implications of ARC for Dosing of Glycopeptides

Despite a greater understanding of the relevant pharmacokinetic-pharmacodynamic properties of vancomycin, the optimal dosing regimen in the critically ill remains uncertain. Present levels of bacterial resistance suggest that trough concentrations of at least 15–20 mg/L are required, and in those displaying ARC, an increased frequency of dosing or continuous infusion may be appropriate. Using Monte Carlo simulations, previous studies have demonstrated that doses higher than those routinely prescribed in the ICU are needed to achieve the desired pharmacokinetic-pharmacodynamic targets, particularly with intermediate

or drug-resistant strains.[35] As with β-lactams, continuous infusion has been proposed as a mechanism to achieve target steady-state concentrations. Although a large, prospective, multicentre study of intermittent dosing versus continuous infusion of glycopeptides failed to show any significant difference in microbiological or clinical outcomes,[151] Rello et al.[152] described a clinical benefit of continuous infusion in critically ill patients with VAP. As ARC significantly impacts on the elimination of vancomycin in subsets of critically ill patients, further research is urgently needed in this area.

Standard dosing strategies for teicoplanin in the critically ill employ a loading dose of 6 mg/kg 12-hourly for three doses,[150] followed by 6 mg/kg 24-hourly thereafter. However, recent work has recommended higher loading doses in hospitalized patients with sepsis,[153] likely as a result of an increased volume of distribution (V_d). In addition, doses of at least 12 mg/kg are required in endocarditis and in bone and joint infections,[154] and have also been advocated in VAP to achieve sufficient trough concentrations in lung tissue.[155]

2.3 Fluoroquinolone Antibacterials

This group of antibacterials includes ciprofloxacin, moxifloxacin, gatifloxacin and levofloxacin. Although a C_{max}/MIC ratio >10 is critical for bacterial eradication,[156] Forrest et al.[89] have concluded that achieving an AUC_{24}/MIC ratio >125 is associated with improved clinical outcomes in critically ill patients with Gram-negative infections. An AUC_{24}/MIC ratio >100 also appears to prevent the emergence of bacterial resistance, particularly in the critically ill.[157]

Currently, there are limited data examining the impact of ARC on fluoroquinolone clearances in the critically ill, although it must be recognized that the effect may be limited, particularly as these agents have a large V_d. Data do exist, however, for ciprofloxacin[158,159] and levofloxacin[160] in this setting.

2.3.1 Implications of ARC for Dosing of Fluoroquinolones

The implications of ARC for dosing of this class of antibacterials is poorly understood. In patients with normal serum creatinine concentrations, we have previously shown that 8-hourly administration of ciprofloxacin was well tolerated and effective in severe sepsis,[161] although this regimen is still unlikely to reach the desired pharmacokinetic-pharmacodynamic targets.[162] Higher doses or alternative dosing regimens may be recommended in the future. In addition, there is a growing evidence base for higher doses of levofloxacin in the critically ill,[163] particularly as this agent is renally excreted. Further research is

needed to address the paucity of knowledge in this area, given the apparent effect of ARC on some fluoroquinolones. Furthermore, suboptimal dosing of fluoroquinolones has been shown to promote the growth of drug-resistant mutants[126] and may be enhanced by rapid drug elimination.

2.4 Aminoglycoside Antibacterials

Aminoglycoside antibacterials demonstrate concentration-dependent killing, are excreted almost entirely unchanged by glomerular filtration[164] and demonstrate comparable, if not superior, clinical outcomes with single versus multiple daily dosing.[165,166] However, doses of 7 mg/kg confer a C_{max}/MIC ratio of at least 10 (maximizing bacterial killing);[167] thus, in the setting of ARC, an increase in the dosing frequency to 18-hourly should be considered. This is particularly relevant in the critically ill, where investigators have demonstrated a significant impact of ICU interventions on pharmacokinetic parameters,[86] in addition to augmented drug clearances in sepsis,[168] haematological malignancy[169] and burns.[170] Recent work has confirmed that traditional dosing regimens are unlikely to meet the required pharmacokinetic-pharmacodynamic targets in the critically ill,[171] likely due to changes in the V_d in this population. As therapeutic drug monitoring is regularly employed in this setting, the impact of ARC can be clearly observed and dosing can be modified appropriately.

2.5 ARC Demonstrated with Other Antibacterials

ARC is likely to be relevant for any renally excreted antibacterial agent prescribed in the critically ill, particularly those agents that demonstrate time-dependent bacterial killing. Daptomycin is a novel lipopolypeptide antibacterial with good activity against most Gram-positive pathogens. Dose reduction has been recommended in patients with moderate to severe renal impairment,[172] as the primary route of elimination is via the kidneys. Currently, there are no data examining the impact of ARC on its prescription in the critically ill, although this may be of limited importance, as bacterial killing appears to be concentration dependent.[173] A lack of ARC was recently demonstrated in a study of febrile neutropenic patients compared with data from other patient populations.[174]

Linezolid is an oxazolidinone antibacterial with activity against multi-resistant Gram-positive pathogens. It is mostly hepatically metabolized before being renally cleared,[175] and dose modification is not currently recommended in patients with renal dysfunction.[176] However, previous data have confirmed time-dependent bacterial killing,[177,178] and a recent

trial of alternate dosing strategies in the critically ill confirmed a pharmacokinetic advantage of continuous infusions in this population.[179] Increased total drug clearance was reported by the authors[179] and may represent augmented hepatic blood flow and/or function, in a manner similar to that of ARC. However conflicting data have been presented by others, suggesting that there is no difference in key tissue and plasma pharmacokinetic parameters in patients suffering from severe sepsis and septic shock compared with healthy subjects.[180]

3. Therapeutic Drug Monitoring

With increasing knowledge of the pharmacokinetic-pharmacodynamic properties of many antibacterials and the ability to measure plasma concentrations with relative precision, therapeutic drug monitoring (TDM) has a crucial role in optimizing antibacterial prescription in the critically ill. TDM is well established for aminoglycosides, where C_{max} and trough concentration monitoring can be used to limit toxicity and improve efficacy.[181] In addition, trough concentrations can be used to guide vancomycin and teicoplanin prescriptions, in order to ensure adequate plasma concentrations.[29,182,183] However, outside these situations, TDM has played only a minor role in monitoring the adequacy of therapy with other routinely prescribed agents.

The significant pathophysiological changes encountered in the critically ill – and, in particular, the recognition of ARC – require the clinician to consider alternate dosing strategies for many agents. TDM represents a useful tool to enable accurate and timely dose modification to achieve the desired pharmacokinetic-pharmacodynamic targets and may significantly improve the clinical efficacy of antibacterial therapy in this population. In addition, the dynamic nature of critical illness and rapid changes in organ function mandate that dosing schedules be consistently evaluated, in order to reduce the likelihood of therapeutic failure or toxicity. As such, TDM should be regarded as an essential component of this process and must be readily available for a wide range of agents in the critical care environment.

4. Conclusions

Determining the optimal dosing regimen for any pharmaceutical is important but is of particular relevance for agents where the clinical response is difficult to assess. In addition, administering 'the right dose' is paramount where any delay in achieving therapeutic concentrations will result in increased morbidity and mortality. Such is the case with the prescription of antibacterials in the critically ill.

Accurate assessment of renal function in this setting is a complex task and usually focuses on identifying renal dysfunction, using regular estimation of serum creatinine concentrations. However, a growing literature base reinforces the hypothesis that 'normal' serum creatinine values may be associated with augmented clearances, particularly in young patients without pre-existing co-morbidity. Previous data have also identified several limitations in a number of commonly used equations to estimate the GFR in the critically ill. As such, a timed urinary creatinine collection remains the most accurate and routinely available method of assessing renal function in this population and should be employed routinely at the clinical level.

The likely mechanisms underlying this phenomenon involve an innate immune response characterized by SIRS and driven by endogenous mediator release. In the critically ill, this is further compounded by administration of intravenous fluids and vasoactive medications. Current evidence highlights young trauma patients as a population particularly 'at risk' although, to date, increasing drug doses in response to higher clearances has seldom been considered.

The implications in terms of enhanced drug elimination are significant, and subtherapeutic concentrations for lengthy periods of the dosing interval may predispose to treatment failure and/or emergence of resistant organisms. As this has largely been neglected in the clinical arena, more frequent estimations of CL_{CR} and TDM are warranted to allow optimization of individual dosing requirements. Further research should now focus on identifying readily measurable predictors of ARC in the critically ill, validation of bedside tests to allow more frequent measurement and empirical adjustment of dosing regimens in this setting.

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